Regulatory Lessons Learned from Ciprofloxacin for Anthrax

for post-exposure prophylaxis
(vs. treatment of established disease)

Filovirus Animal Model Workshop
September 12, 2007

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Outline

- Introduction
  - Anthrax
  - Ciprofloxacin
- Inhalational anthrax
  - How ciprofloxacin was approved for post exposure prophylaxis of inhalational anthrax
- Treatment of inhalational anthrax
  - Challenges in evaluating antitoxins

Introduction

- Ciprofloxacin approved for post-exposure prophylaxis of inhalational anthrax on **August 30, 2000**
  - **Inhalational anthrax** (post-exposure): To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis.**
  - Adult: 500 mg PO 12 h for 60 Days
    - or 400mg IV q12
  - Pediatric: 15 mg/kg PO per dose q12h for 60 Days
    - or 10 mg/kg per dose IV

*Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication. (See also, INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION).

Anthrax

- Bacterial infection caused by *B. anthracis*
  - Cutaneous, inhalational, gastrointestinal disease
  - CDC Category A bioterrorism agent
  - Susceptible to penicillin and doxycycline, concerns about bioengineered resistant organisms
  - Capsule, PA, EF, LF
- Rare
  - One patient 2006
  - In October 2001, 22 cases reported
    - 6/11 patients inhalational anthrax survived
    - 11/11 with cutaneous anthrax and survived
  - 1979, Sverdlovsk accidental release of spores
    - 60+ deaths
    - 42 cases provided information on pathology*

*Abramova FA, Grinsberg LM, Yampolskaya OV, Walter DH. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak of 1979. Proc Natl Acad Sci USA 1993:90-2291-4.

Ciprofloxacin

- Fluoroquinolone antimicrobial
  - Marketed since 1987
  - Available in oral and IV form
  - Approved for multiple indications
    - Including respiratory, skin, bone, and typhoid fever (reticuloendothelial system-macrophage/monocyte)
  - Millions of human exposures
  - Safety for 60 days or longer in adults and pediatric patients (osteomyelitis, CF, etc)

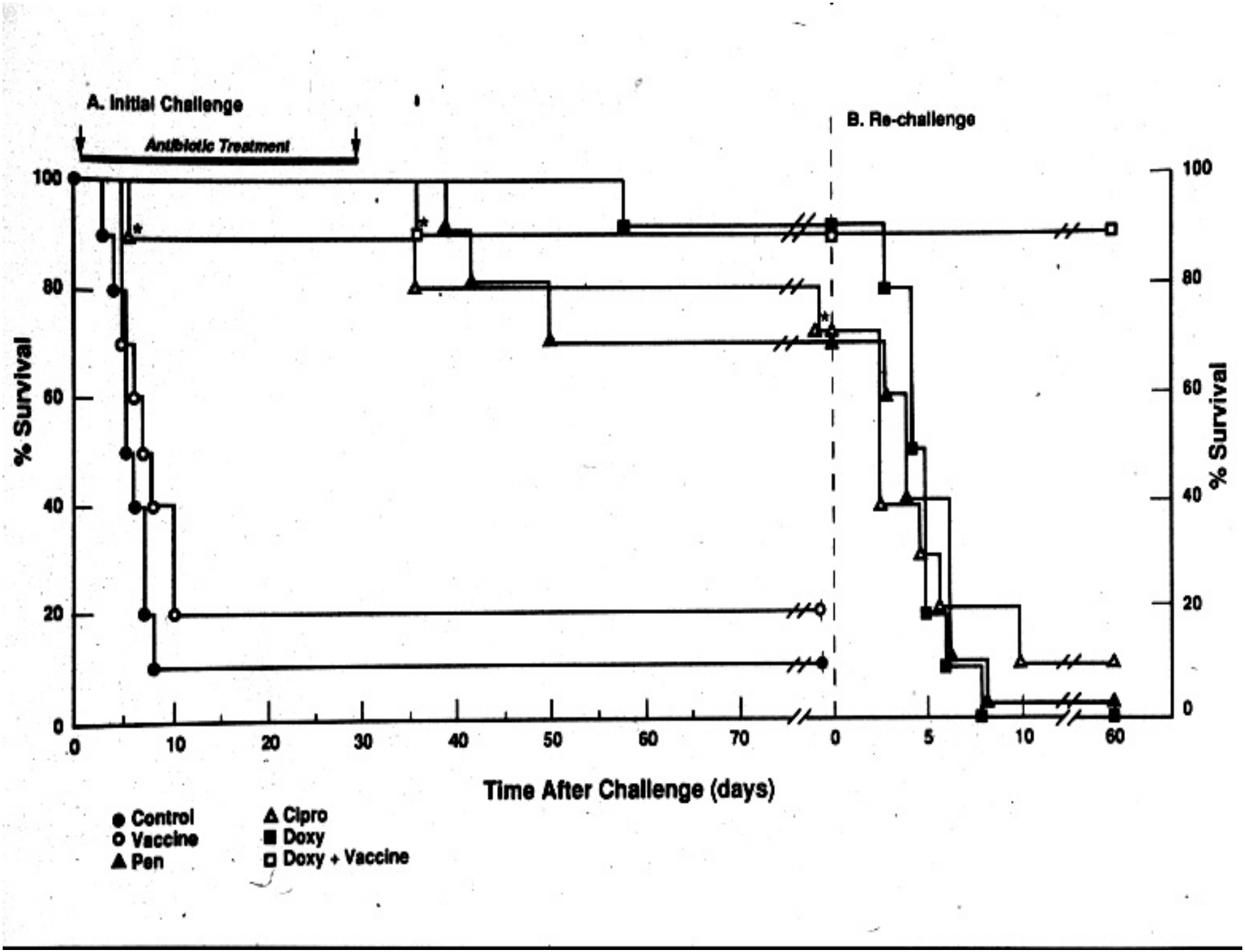
Inhalational anthrax

Post exposure prophylaxis

Efficacy of ciprofloxacin

- Clinical studies in humans not possible
- Animal Model of Infection
  - Rhesus macaque
  - Used in Friedlander 1993 study, USAMRIID
  - Why was the NHP acceptable to support post-exposure prophylaxis indication?
    - Similaries between human and NHP

*Friedlander, AM, Welkos, SL, Pitt LM. et al., Postexposure Prophylaxis Against Experimental Inhalation Anthrax, Journal of Infectious Diseases, **1993**; 167:1239-1243.


A. Initial Challenge
Antibiotic Treatment
B. Re-challenge
% Survival
100
80
60
40
20
0
0
10
20
30
40
50
60
70
0
5
10
60
Time After Challenge (days)
Control
Vaccine
Pen
Cipro
Doxy
Doxy + Vaccine

NHP vs Human disease: similarities

- Pathogen
  - *Bacillus anthracis* (Vollum strain)
  - In 2001 *B. anthracis* Ames strain
  - In subsequent levofloxacin study, Ames strain
- Exposure to pathogen
  - Route of infection via aerosol
  - Spores delivered to lungs
  - Multiples of LD_{50}

Disease similarities

- Course/Pathogenesis of disease following exposure, without antimicrobial
  - Time course – rapidly fatal
  - (Signs and symptoms)
  - Bacteremia, Toxemia
  - Outcome
    - Survival low
    - Mortality high
    - Confirmed anthrax

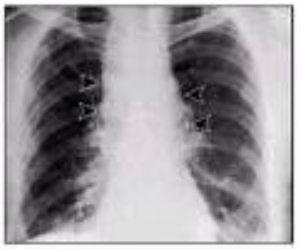
Drug Administration similarities

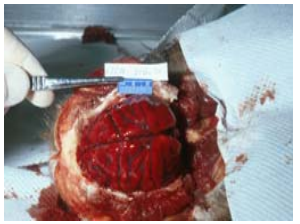
- Ciprofloxacin
- Human dosing regimen
  - Various treatment regimens approved in humans
  - 500 mg q12h PO x 60 days previously used
- Animals received ciprofloxacin via same route & frequency
  - Oral
  - Q12h hours
  - 125 mg per animal
- Intervention – 24 hours after exposure to *B. anthracis* spores

Pharmacokinetic similarities

- Adult (500 mg)
  - Cmax 2.89 mcg/mL, Cmin 0.28 mcg/mL, AUC 27.9 mcg*hr/mL
- Pediatric (15 mg/kg)
  - Cmax 3.5 mcg/mL, AUC 27 mcg*hr/mL
- Rhesus macaque (125 mg)
  - Cmax 0.98-1.55 mcg/mL, Cmin 0.11-0.18 mcg/mL

Outcome similarities





- Findings in controls
  - Rapid down-hill course
  - Mediastinal widening – hilar nodes
  - Meningeal involvement
- High mortality
- Edema, hemorrhage and necrosis is affected tissued
  - Toxin mediated, EF and LF

Efficacy of ciprofloxacin in NHP

	Ciprofloxacin	Saline control	P value
Anthrax deaths	1/9*	9/10	0.0011

The anthrax death occurred at d 36, 6 days after discontinuing ciprofloxacin – no deaths occurred while animals were receiving antimicrobials

One animal died due to gavage accident and did not have anthrax

Summary of similarities

- Pathogen
- Route of Exposure
- Course of Disease
- Drug administration
- Pharmacokinetics
- Outcome
- Findings

Ciprofloxacin - approval

- Advisory Committee meeting **July 28, 2000***
- All information presented and reviewed
- Approved under 21 CFR Subpart H, 314.510**
  - "Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication."
  - Applicant fulfilled Phase 4 requirement with data from 2001 anthrax events

*http://www.fda.gov/cder/drug/infopage/cipro/

**Corresponding section for biologics: 21 CFR Subpart E, 601.41

Other approvals

- Doxycycline/Penicillin G
  - Already approved for anthrax
  - FR Notice **November 2, 2001** (p 55679) extended labeling of PEP
    - Doxycycline 100 mg bid for adults; 1 mg/lb (2.2 mg/kg); PO or IV for 60 days.
    - Pen G procaine 1,200,000 units q12h in adults, 25,000 units/kg q12h in children
      - increased incidence of serum sickness-like reactions associated with use of penicillin for more than 2 weeks.
- Levofloxacin …

Levofloxacin

- FQ antimicrobial, marketed since 1996
  - Efficacy in multiple indications
  - Safety in millions of adults, maximum 28 days based on AWC studies (lacking in pediatric patients)
  - Dosed 500 mg QD dose
- Non human primate
  - Rapid clearance of levofloxacin, needed BID dosing
  - Use of hollow fiber to model doses
  - Daily 15 mg/kg (0h), followed by 4 mg/kg (12h) x 30 days

Levofloxacin - approval

- Approved for PEP on **November 24, 2004**
  - Efficacy based on extrapolation from NHP
    - Subpart H surrogate endpoint
    - 500 mg qd x 60 days*
  - Only enough for adult safety for 28 days, labeling reflects this information
    - *The safety of levofloxacin in adults for durations of therapy beyond 28 days has not been studied. Prolonged levofloxacin therapy in adults should only be used when the benefit outweighs the risk
  - No safety data for pediatric patients provided

http://www.fda.gov/cder/drug/infopage/levaquin/default.htm

Regulatory approach to approval

- Animal model of infection and human infection similarities
- Ciprofloxacin levels achieved in NHP were protective
  - Reduced mortality in placebo controlled study
  - Exceeded MIC of organism
- These levels were achieved in humans
  - Levels served as surrogate endpoint to support that ciprofloxacin would protect humans in the event of exposure to *B. anthracis*
- Subpart H approval
  - “Ciprofloxacin serum concentrations achieved in humans serve as a surrogate endpoint reasonably likely to predict clinical benefit and provide the basis for this indication. (See also, INHALATIONAL ANTHRAX – ADDITIONAL INFORMATION).“

Inhalational anthrax (IA)

treatment of established disease

Inhalational anthrax disease:

treatment once infection is established

- Characterized by bacteremia & toxemia in humans
  - October 2001, 5/11 patients died
  - Antimicrobials alone not sufficient
  - Need antitoxin product to be evaluated
- Animal model of infection
  - Need to identify animal model of infection and intervene at the time the animal has established disease
    - Animals do not reliably have prodrome
    - When to intervene?
  - Disease diagnosis may be based on bacteremia and toxemia

Established IA disease in human vs animal: What are the similarities?

- Pathogen ✓
- Route of Exposure ✓
- Course of Disease ✓
  - Time to intervention ?
- Drug/product ? Administration ?
- Pharmacokinetics – ?
- Outcome ✓

Challenges

- Disease – difficulty in determining when disease has become established
  - Rabbit studies suggest around 24-36 hours, include some lab findings
  - Non human primate may be less predictable
- Need animal model(s) of infection to be developed
  - Reliable, reproducible

Current thinking

- Treatment – timing of intervention is challenging (too soon vs too late)
  - When bacteremia / toxemia is present
- Antitoxin therapies are not approved, thus despite similarities between human and animal disease, need 2 species to demonstrate efficacy*
  - Studies need to demonstrate antitoxin product is superior to placebo
  - Studies should also evaluate treatment with antitoxin plus antimicrobial

*Summary of “animal rule” in backup slides

Challenges that have been stated

(therefore studies should be well thought and well conducted to maximize information obtained)

- Limited number of animals available
- Limited number of study sites available
- Need for BL4 labs
- Resource intensive
  - Multiple procedures for each animal
  - 24 hour monitoring
-

Summary

- Drugs for inhalational anthrax, post-exposure prophylaxis
  - Ciprofloxacin, levofloxacin, doxycycline and pen G
  - 21 CFR 314.500, Subpart H of regulations
- Products for treatment of inhalational anthrax established disease (antitoxins)
  - Challenging
  - Animal rule

Questions?

White Oak Office Building 22

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Evidence needed to demonstrate effectiveness of New Drugs (or Biologics) when human efficacy studies are not ethical or feasible [Animal Rule]*

*FR May 31, 2002 p37988

Final Rule effective July 1, 2002

Animal Rule

- Subpart I Approval of Drugs When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR 314.600
  - (1) There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
  - (2) The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
  - (3) The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and
  - (4) The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans

*FR May 31, 2002 p37988; Final Rule effective July 1, 2002

Animal Rule

- Subpart I Approval of Biological Products When Human Efficacy Studies Are Not Ethical or Feasible
- 21 CFR 314.600
  - Postmarketing studies
  - Approval with restrictions to safe use
    - (i) Distribution restricted to certain facilities or health care practitioners with special training or experience;
    - (ii) Distribution conditioned on the performance of specified medical procedures, including medical follow up; and
    - (iii) Distribution conditioned on specified recordkeeping requirements.
  - Information to be provided to patient recipients

*FR May 31, 2002 p37988; Final Rule effective July 1, 2002

Animal Rule

- “We have decided to eliminate the requirement that ‘products would be expected to provide meaningful therapeutic benefits’ to patients over existing treatments”
  - Anthrax 2001 events indicate need for wide range of therapeutic options
  - Allergies and other adverse events
  - Availability
  - [Resistance]

Safety

- Animal rule
  - “safety evaluation of products in not addressed under this rule”
  - “products evaluated for effectiveness under subpart I for part 314 and subpart H of 601 will be evaluated for safety under preexisting requirements for establishing the safety of new drug and biologic products.”
    - Human volunteers
    - Some data (interaction between toxic substance and product) may not be available

Anthax – *Bacillus anthracis*

- Information from publicly available sources
  - Anthim™ mAb (ETI-204) to PA, Infection and Immunity 2005; 73(2):795-802 (Elusys)
  - Heteropolymer binds PA in vitro, presented at 5th international conference on anthrax, Nice, France (Elusys)
  - ABthrax™ (PAmAb) fully human mAb against PA in Phase 1 study in healthy volunteers, CID 2005;41:12-20. (HGS)
  - Valortim™ humanized ab to PA, presented at IDSA (Medarex and PharmAthene)